National Toxicology Program
Toxicity Report Series
Number 47

NTP Technical Report on the Toxicity Studies of

Methacrylonitrile

(CAS No. 126-98-7)

Administered by Gavage to F344/N Rats and B6C3F$_1$ Mice

May 2000

U.S. Department of Health and Human Services
Public Health Service
National Institutes of Health

FOREWORD

The National Toxicology Program (NTP) is made up of four charter agencies of the U.S. Department of Health and Human Services (DHHS): the National Cancer Institute (NCI), National Institutes of Health; the National Institute of Environmental Health Sciences (NIEHS), National Institutes of Health; the National Center for Toxicological Research (NCTR), Food and Drug Administration; and the National Institute for Occupational Safety and Health (NIOSH), Centers for Disease Control and Prevention. In July 1981, the Carcinogenesis Bioassay Testing Program, NCI, was transferred to the NIEHS. The NTP coordinates the relevant programs, staff, and resources from these Public Health Service agencies relating to basic and applied research and to biological assay development and validation.

The NTP develops, evaluates, and disseminates scientific information about potentially toxic and hazardous chemicals. This knowledge is used for protecting the health of the American people and for the primary prevention of disease.

The studies described in this Toxicity Study Report were performed under the direction of the NIEHS and were conducted in compliance with NTP laboratory health and safety requirements and must meet or exceed all applicable federal, state, and local health and safety regulations. Animal care and use were in accordance with the Public Health Service Policy on Humane Care and Use of Animals.

These studies are designed and conducted to characterize and evaluate the toxicologic potential of selected chemicals in laboratory animals (usually two species, rats and mice). Chemicals selected for NTP toxicology studies are chosen primarily on the bases of human exposure, level of production, and chemical structure. The interpretive conclusions presented in this Toxicity Study Report are based only on the results of these NTP studies. Extrapolation of these results to other species and quantitative risk analyses for humans require wider analyses beyond the purview of these studies. Selection *per se* is not an indicator of a chemical's toxic potential.

Listings of all published NTP reports and ongoing studies are available from NTP Central Data Management, NIEHS, P.O. Box 12233, MD E1-02, Research Triangle Park, NC 27709 (919-541-3419). Other information about NTP studies is available at the NTP's World Wide Web site: http://ntp-server.niehs.nih.gov.

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Burhan I. Ghanayem, Ph.D., Study Scientist

May 2000

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CONTRIBUTORS

National Toxicology Program
Evaluated and interpreted results and reported findings

B.I. Ghanayem, Ph.D., Study Scientist
J.R. Bucher, Ph.D.
R.E. Chapin, Ph.D.
R.S. Chhabra, Ph.D.
M.R. Elwell, D.V.M., Ph.D.
J. Mahler, D.V.M.
C.S. Smith, Ph.D.
G.S. Travlos, D.V.M.
K.L. Witt, M.S., Integrated Laboratory Systems, Inc.

Battelle Columbus Laboratories
Conducted studies and evaluated pathology findings

P.J. Kurtz, Ph.D., Principal Investigator
G.B. Freeman, Ph.D.
M.J. Ryan, D.V.M., Ph.D.
J.D. Toft II, D.V.M., M.S.
J.T. Yarrington, D.V.M., Ph.D.

NTP Pathology Review
Evaluated slides and prepared pathology report (11 October 1994)

J.C. Seely, D.V.M., Chairperson
Pathology Associates International
J. Mahler, D.V.M.
National Toxicology Program

Experimental Pathology Laboratories, Inc.
Provided pathology quality assessment

S. Botts, D.V.M., Ph.D.
M. Wells, D.V.M.

Environmental Health Research and Testing, Inc.
Provided sperm motility and vaginal cytology evaluations

T. Cocanougher, B.A.
D.K. Gulati, Ph.D.
S. Russell, B.A.

Analytical Sciences, Inc.
Provided statistical analyses

R.W. Morris, M.S., Principal Investigator
K.P. McGowan, M.B.A.
M.A. Mauney, M.S.
N.G. Mintz, B.S.
J.T. Scott, M.S.

Biotechnical Services, Inc.
Prepared Toxicity Study Report

S.R. Gunnels, M.A., Principal Investigator
A.M. Macri-Hanson, M.A., M.F.A.
W.D. Sharp, B.A., B.S.
S.M. Swift, B.S.
R.A. Willis, B.A., B.S.

PEER REVIEW

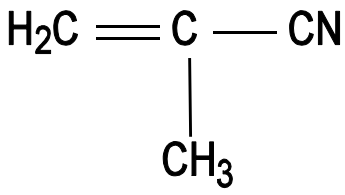
The draft report on the toxicity studies of methacrylonitrile was evaluated by the reviewers listed below. These reviewers serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, reviewers determine if the design and conditions of these NTP studies are appropriate and ensure that this toxicity study report presents the experimental results and conclusions fully and clearly.

Dr. Gary Carlson, Ph.D.
School of Health Sciences
Purdue University
West Lafayette, IN

Dr. Mohammed Y.H. Farooqui, Ph.D.
Department of Biology
University of Texas Pan American
Edinburg, TX

CONTENTS

ABSTRACT



Methacrylonitrile

CAS No. 126-98-7

Chemical Formula: C_4H_5N Molecular Weight: 67.09

Synonyms: 2-Cyano-propene; 2-cyano-1-propene; isopropene cyanide; isopropenyl nitrile; MAN; methyl acrylonitrile; 2-methyl-2-propenenitrile

Methacrylonitrile is an aliphatic nitrile used extensively in the preparation of homo- and copolymers, elastomers, and plastics and as a chemical intermediate in the preparation of acids, amides, esters, and other nitriles. This aliphatic nitrile is also used as a replacement for acrylonitrile in the manufacture of an acrylonitrile/butadiene/styrene-like polymer. Methacrylonitrile was nominated for toxicity and carcinogenicity testing by the National Cancer Institute due to its high production volume and extensive use, the lack of chronic or carcinogenicity data, and its structural resemblance to the known rat carcinogen acrylonitrile. The current 13-week studies were conducted as part of an overall effort by the NTP to assess the toxicity and carcinogenicity of methacrylonitrile.

During the 13-week studies, groups of 20 male and 20 female F344/N rats were administered 0, 7.5, 15, 30, 60, or 120 mg methacrylonitrile/kg body weight in deionized, purified water by gavage. Groups of 20 male and 20 female B6C3F$_1$ mice were administered 0, 0.75, 1.5, 3, 6, or 12 mg/kg methacrylonitrile. Ten male and ten female rats and mice from each group were evaluated on day 32.

The results of these studies clearly revealed that male rats are more sensitive than females to methacrylonitrile treatment. In the rat study, 19 males and one female administered 120 mg/kg and two males administered 60 mg/kg died during the first week of the study. Males in the 60 mg/kg group at the 32-day interim evaluation and at 13 weeks and females in the 120 mg/kg group at 13 weeks had significantly lower final mean body

weights and body weight gains than did the vehicle controls; the surviving male in the 120 mg/kg group also weighed less than the controls at the 32-day interim evaluation. Clinical findings of toxicity were dose dependent and included lethargy, lacrimation, tremors, convulsions, ataxia, and abnormal breathing.

There was hematologic evidence indicating that administration of methacrylonitrile induced minimal, normocytic, normochromic anemia. At the 32-day interim evaluation, a minimal dose-related anemia was evidenced by decreases in hematocrit values, hemoglobin concentrations, and erythrocyte counts in male and female rats. The anemia ameliorated by week 13. Administration of methacrylonitrile resulted in dose-related increases in serum thiocyanate and blood cyanide concentrations of male and female rats. These changes were expected and would be consistent with the *in vivo* metabolism of methacrylonitrile to cyanide. Blood cyanide concentrations were generally higher in males than in females, which may explain the higher sensitivity of males to the lethal effect of methacrylonitrile. There was also biochemical evidence of increased hepatocellular leakage and/or altered function in dosed male rats, suggesting that the liver may be a target organ for toxic effects of methacrylonitrile.

Minimal, but significant, decreases in absolute right kidney and thymus weights (32-day interim evaluation) and increases in liver and stomach weights (week 13) occurred in male rats that received 60 mg/kg compared to the vehicle controls. In female rats, stomach weights of the 60 and 120 mg/kg groups were significantly greater and thymus weights of the 120 mg/kg group were significantly less than those of the controls on day 32 and at week 13; liver weights were also significantly greater in females in the 120 mg/kg group than in the vehicle controls on day 32.

Male and female rats administered 60 mg/kg and females administered 120 mg/kg had significantly greater incidences of metaplasia of the nasal olfactory epithelium on day 32 and at the end of the study than did the vehicle controls; incidences of olfactory epithelial necrosis were also significantly greater in females in the 60 and 120 mg/kg groups than in the vehicle controls on day 32. Incidence and/or severity increased with increasing dose in females; however, the mortality in male rats administered 120 mg/kg made it difficult to assess the dose-response relationship in males. The no-observed-adverse-effect level for the nasal cavity of rats was 30 mg/kg.

Female rats administered 60 or 120 mg/kg methacrylonitrile had significantly longer estrous cycles than did the vehicle controls. Females in the 60 mg/kg group spent more time in diestrus than the vehicle controls.

One male and one female mouse in the 12 mg/kg groups died early. Methacrylonitrile administration caused no significant differences in final mean body weights or body weight gains. Clinical findings included lethargy, tremors, ataxia, convulsions, and abnormal breathing. At the 32-day interim evaluation, stomach weights of males administered 3 mg/kg or greater were significantly greater and thymus weights of males in the 12 mg/kg group were significantly less than those of the vehicle controls. At week 13, however, the stomach weights of only males in the 12 mg/kg group were increased relative to the vehicle controls. No treatment-related histopathologic lesions occurred in mice.

Methacrylonitrile did not induce mutations in any of several strains of *Salmonella typhimurium*, with or without S9 activation, and did not induce sex-linked recessive lethal mutations in germ cells of male *Drosophila melanogaster* fed methacrylonitrile during the larval stage. Results of *in vivo* bone marrow micronucleus tests with methacrylonitrile in male rats and mice were also negative.

In summary, gavage administration of methacrylonitrile to rats and mice resulted in dose-dependent lethargy, tremors, lacrimation, convulsions, and abnormal breathing. However, these effects were more pronounced in rats than mice; these differences may be attributed to the higher doses of methacrylonitrile administered to rats. Body weight gain and survival data of rats demonstrated that males are more sensitive to methacrylonitrile dosing than females. There is an apparent correlation between blood cyanide concentrations and survival rates, with males having greater cyanide concentrations and lower survival rates than female rats administered methacrylonitrile. Microscopically, the only target of methacrylonitrile toxicity was the olfactory epithelium of the nasal cavity. Necrotic and metaplastic effects were induced in male and female rats that received 60 or 120 mg/kg per day. No similar lesions were observed in mice administered methacrylonitrile. The no-observed-adverse-effect level for olfactory epithelial lesions in male and female rats administered methacrylonitrile for 13 weeks was 30 mg/kg per day. No clear chemical-related effects were observed in male or female mice administered methacrylonitrile for 13 weeks by gavage at doses up to 12 mg/kg per day.